ONE-POT REGIOSPECIFIC SYNTHESIS OF NEW SUBSTITUTED 1,4-BENZOXAZINES THROUGH AN INVERSE ELECTRON-DEMAND HETERO DIELS-ALDER REACTION OF SIMULTANEOUSLY ELECTROGENERATED DIENE AND DIENOPHILE.

MARTINE LARGERON, MARC VUILHORGNE[#], ESTELLE BLATTES, ANNE NEUDORFFER AND MAURICE-BERNARD FLEURY

LABORATOIRE DE CHIMIE ANALYTIQUE ET ELECTROCHIMIE, UMR 8638 CNRS-UNIVERSITE RENE DESCARTES, FACULTE DES SCIENCES PHARMACEUTIQUES ET BIOLOGIQUES, 4, AVENUE DE L'OBSERVATOIRE, 75270 PARIS, CEDEX 06, FRANCE

[#]AVENTIS PHARMA, CENTRE DE RECHERCHE DE VITRY-ALFORTVILLE, 13, QUAI JULES GUESDE 94403 VITRY-SUR-SEINE, FRANCE

Recently, we have evidenced the reaction of a new type of quinonoid system with benzylamine, in order to mimic the reactions occurring in the course of the enzymatic oxidation of amines by quinone cofactors like pyrroloquinoline quinone (**PQQ**) or topaquinone (**TPQ**) (1-3). Thus, we have demonstrated that electrogenerated 3,4-iminoquinone $\mathbf{1_{ox}}$ acts as an efficient catalyst for the autorecycling oxidation of benzylamine; the reaction efficiency reached 64 turnovers.

Additional mechanistic investigations revealed that the deamination mechanism of benzylamine by our model system $\mathbf{1_{ox}}$ was akin to the transamination reaction of pyridoxal phosphate with amino-acids (4). This involved a tautomerization of the benzyliminoquinone species to the product Schiff base, which, after addition of benzylamine, was converted into 3,4-aminophenol $\mathbf{1_{red}}$ and N-benzylidene-benzylamine (Scheme 1).

The reaction was further extended to aliphatic amines. In some cases (isobutylamine, for example), the reaction efficiency could not exceed 8 turnovers, owing to the conversion of catalyst $\mathbf{1_{ox}}$ to novel 1,4-benzoxazine derivatives, probably through a regiospecific inverse electron-demand Diels-Alder reaction (Scheme 2). This involved 3,4-iminoquinone $\mathbf{1_{ox}}$ as the diene and enamine (tautomeric form of the imine extruded during the catalytic process), as the dienophile, both being simultaneously electro-generated.

This unexpected reaction should provide a mild and concise route to novel substituted 1,4-benzoxazine derivatives, which could be effective as neuroprotective agents (5).

REFERENCES

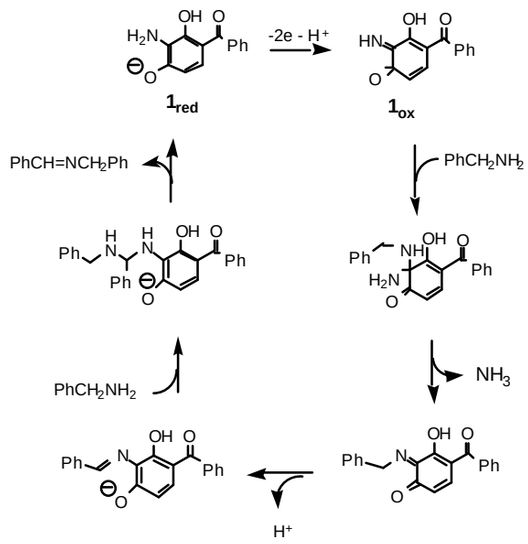
1. S. Itoh, N. Takada, T. Ando, S. Haranou, X. Huang, Y. Uenoyama, Y. Ohshiro, M. Komatsu and S. Fukuzumi, J. Org. Chem., **62**, 5898 (1997) and references therein.

2. Y. Lee and L.M. Sayre, J. Am. Chem. Soc., **117**, 3096 (1995).

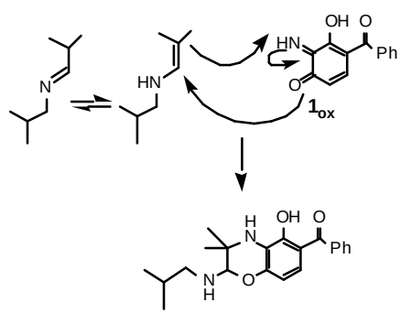
3. M. Mure and J.P. Klinman, J. Am. Chem. Soc., **117**, 8707 (1995).

4. M. Largeron and M.-B. Fleury, J. Org. Chem., **65**, 8874 (2000).

5. M. Largeron, B. Lockhart, B. Pfeiffer and M.-B. Fleury, J. Med. Chem., **42**, 5043 (1999).



Scheme 1



Scheme 2